British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 2148–2162 2148

SYSTEMATIC REVIEW AND META–ANALYSIS

Aprepitant and fosaprepitant drug interactions: a systematic review

Correspondence L. Lee Dupuis RPh, PhD, Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, 555 University Ave, Toronto, Ontario, Canada M5M 1X3. Tel.: +1 416 813 7654 ext 309355; Fax: +1 416 813 5979; E-mail: lee.dupuis@sickkids.ca

Received 5 January 2017; **Revised** 12 April 2017; **Accepted** 21 April 2017

Priya Patel[1,2], J. Steven Leeder[3,4], Micheline Piquette-Miller[1] and L. Lee Dupuis[1,2,5]

[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada, [2]Department of Pharmacy, The Hospital for Sick Children, Toronto, Ontario, Canada, [3]Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Department of Pediatrics, Children's Mercy-Kansas City, Kansas City, Missouri, USA, [4]School of Medicine, University of Missouri-Kansas City, Kansas City, Missouri, USA, and [5]Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada

Keywords aprepitant, drug–drug interactions, fosaprepitant

AIMS

Aprepitant and fosaprepitant, commonly used for the prevention of chemotherapy-induced nausea and vomiting, alter cytochrome P450 activity. This systematic review evaluates clinically significant pharmacokinetic drug interactions with aprepitant and fosaprepitant and describes adverse events ascribed to drug interactions with aprepitant or fosaprepitant.

METHODS

We systematically reviewed the literature to September 11, 2016, to identify articles evaluating drug interactions involving aprepitant/fosaprepitant. The clinical significance of each reported pharmacokinetic drug interaction was evaluated based on the United States Food and Drug Administration guidance document on conducting drug interaction studies. The probability of an adverse event reported in case reports being due to a drug interaction with aprepitant/fosaprepitant was determined using the Drug Interaction Probability Scale.

RESULTS

A total of 4377 publications were identified. Of these, 64 met inclusion eligibility criteria: 34 described pharmacokinetic drug interactions and 30 described adverse events ascribed to a drug interaction. Clinically significant pharmacokinetic interactions between aprepitant/fosaprepitant and bosutinib PO, cabazitaxel IV, cyclophosphamide IV, dexamethasone PO, methylprednisolone IV, midazolam PO/IV, oxycodone PO and tolbutamide PO were identified, as were adverse events resulting from an interaction between aprepitant/fosaprepitant and alcohol, anthracyclines, ifosfamide, oxycodone, quetiapine, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors and warfarin.

CONCLUSIONS

The potential for a drug interaction with aprepitant and fosaprepitant should be considered when selecting antiemetic therapy.

DOI:10.1111/bcp.13322

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Aprepitant and fosaprepitant are moderate and weak CYP3A4 inhibitors, respectively. Aprepitant is also a weak CYP2C9 inducer.
- There are no systematic literature reviews describing interactions between aprepitant or fosaprepitant and other drugs.

WHAT THIS STUDY ADDS

- Using the FDA's definition, reports of clinically significant pharmacokinetic interactions between aprepitant and bosutinib, cabazitaxel, cyclophosphamide, dexamethasone, methylprednisolone, midazolam, oxycodone and tolbutamide were identified.
- Concurrent administration of aprepitant and the following drugs may lead to adverse events: alcohol (impaired cognition), ifosfamide (neurotoxicity), oxycodone (decreased respiratory rate, increased feeling of a 'high'), quetiapine (somnolence), SSRI/SNRIs (vomiting) and warfarin (INR changes). Administration of fosaprepitant and anthracyclines *via* the same peripheral vein may cause a local reaction at the infusion site.

Tables of Links

TARGETS	
GPCRs [2]	**Enzymes** [3]
NK_1 receptor	CYP3A4
	CYP2C9

LIGANDS	
alcohol	methylprednisolone
aprepitant	midazolam
bosutinib	ondansetron
cabazitaxel	oxycodone
cyclophosphamide	palonosetron
dexamethasone	paroxetine
digoxin	pazopanib
dinaciclib	prednisolone
docetaxel	quetiapine
dolasetron	tacrolimus
erlotinib	thiotepa
fosaprepitant	tolbutamide
granisetron	vinorelbine
ifosfamide	warfarin
melphalan	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Introduction

A neurokinin-1 antagonist such as oral (PO) aprepitant or its intravenous (IV) prodrug, fosaprepitant, together with a 5-HT_3 antagonist and dexamethasone, are strongly recommended for prophylaxis of chemotherapy-induced nausea and vomiting (CINV) in both adult and paediatric cancer patients receiving highly emetogenic chemotherapy [4–7]. However, aprepitant and fosaprepitant are moderate [8, 9] and weak inhibitors of CYP3A4 [10, 11], respectively, and there is uncertainty regarding the clinical significance of potential interactions with CYP3A4 substrates. A moderate CYP3A4 inhibitor may increase the area under the concentration *vs.* time curve (AUC) of a victim drug by two- to up to five-fold and a weak CYP3A4 inhibitor may increase AUC of a victim drug by 1.25- up to two-fold [12]. CYP3A4 inhibitors may also reduce the conversion of a prodrug to its active form [13]. Aprepitant or fosaprepitant may therefore influence the toxicity and the efficacy of concomitantly administered drugs. Recommendations for CINV prevention in children with cancer caution against the use of aprepitant with antineoplastic agents which are CYP3A4 substrates [6, 14]. However, avoidance of aprepitant due to potential interactions with antineoplastic therapy may open patients to uncontrolled CINV.

There is, however, no comprehensive, systematic assessment of the literature describing the extent of interaction between aprepitant or fosaprepitant and other drugs. The primary objective of this systematic review was to describe the pharmacokinetic disposition of drugs co-administered with aprepitant or fosaprepitant using a standard definition of clinical significance. Our secondary objective was to

describe adverse events ascribed to a drug interaction with aprepitant or fosaprepitant. The results of this systematic review will facilitate informed decision making regarding the selection of CINV prophylaxis.

Methods

The Preferred Reporting Items in Systematic Reviews and Meta-Analyses Protocols [15] and the Preferred Reporting Items in Systematic Reviews and Meta-Analyses guidelines [16] were followed in conducting this systematic review. Details on the search methods can be found in Supporting Information Appendix S1 (Tables S1 and S2). The publication selection, data extraction and quality assessment procedures are presented in Supporting Information Appendix S2.

We defined pharmacokinetic drug interactions as clinically significant according to the United States Food and Drug Administration (FDA) guidance document on drug interaction studies [17]. That is, an interaction was clinically significant when: (1) the geometric mean ratio (GMR) for the comparison of a victim drug's maximum concentration (C_{max}) in the presence *vs.* in the absence of aprepitant or fosaprepitant was greater than 1.25 or less than 0.80 or (2) the GMR for the comparison of the AUC of a victim drug in the presence *vs.* in the absence of aprepitant or fosaprepitant was greater than 1.25 or less than 0.80. This definition was based on the GMR for C_{max} or AUC of the victim drug irrespective of the associated confidence interval (CI).

A significant adverse event was defined as an event where a patient experienced discomfort, harm or changes in a laboratory parameter that was indicative of an increased risk for harm that was highly suspected to have occurred due to co-administration of aprepitant or fosaprepitant with the patient's other medications. In the case of comparative studies, a high suspicion of interaction was defined as a statistically significant difference in the rate of the adverse event in the presence of aprepitant or fosaprepitant *vs.* the absence of aprepitant or fosaprepitant. The probability that the findings of case reports were a result of a drug interaction with aprepitant or fosaprepitant was determined using the Drug Interaction Probability Scale (DIPS) [18]. DIPS scores of 5 or greater indicate that a causal relationship between the adverse event and the drug interaction is probable or highly probable.

Results

Publication selection

Our literature search identified 4377 publications. Of these, 122 were brought to full text screening and 65 met criteria to be included in the qualitative synthesis. One publication [19] was excluded because it used methods that would affect the validity and generalizability of study findings. Hence, a total of 64 publications were included in the final synthesis (see Figure 1). Inter-screener agreement was substantial with a calculated kappa of 0.77 (95% CI: 0.65–0.88) [20]. The quality assessment of all included publications (case reports excluded) is reported in Supporting Information Appendix S3 (Tables S3–S5). The DIPS scores of included case reports are presented in Supporting Information Appendix S3 (Table S10).

Publication characteristics

Of the 64 included publications, 34 evaluated pharmacokinetic interactions in adults (aprepitant/fosaprepitant and antineoplastic drug: 14 [21–34]; aprepitant/fosaprepitant and non-antineoplastic drug: 20 [9, 11, 35–52]). Thirty-eight described adverse events in adults potentially resulting from drug interactions with aprepitant or fosaprepitant, eight of which also evaluated for a pharmacokinetic aprepitant/fosaprepitant drug interaction (aprepitant/fosaprepitant and antineoplastic drug: 24 [23, 25, 33, 53–73]; aprepitant and non-antineoplastic drug: 14 [35, 43, 46, 51, 52, 74–82]). In all, 27 victim drugs were evaluated for pharmacokinetic interaction with aprepitant or fosaprepitant and an adverse event was ascribed by study authors to an interaction with aprepitant or fosaprepitant for 15 victim drugs. Table 1 summarizes the characteristics of included publications. Complete data summary tables are provided in Supporting Information Appendix S3 (Tables S6–S9). A summary of findings are presented in Table 2.

Pharmacokinetic interactions with aprepitant or fosaprepitant

Antineoplastic drugs. Thirteen included publications evaluated interactions between aprepitant and 10 individual antineoplastic drugs [21–30, 32–34] and one publication evaluated an interaction between fosaprepitant and ifosfamide [31]. Seven included publications reported a GMR for AUC or C_{max} with and without aprepitant or fosaprepitant, which allowed assessment of clinical significance [27, 29–34]. Of these, three interactions met criteria for clinical significance: bosutinib PO [34], cabazitaxel IV [30] and cyclophosphamide IV [32].

GMR for AUC and C_{max} with/without aprepitant were not reported in the publications describing erlotinib (route not reported) [28], ifosfamide IV [23], melphalan IV [24], pazopanib IV [25], and thiotepa IV disposition [22]. However, significant differences in other pharmacokinetic parameters were reported for several of these drugs when co-administered with aprepitant. Changes in parameters indicative of reduced clearance were reported for CYP3A4 substrates in the presence of aprepitant: erlotinib (two-fold increase in the trough concentration) [28], pazopanib IV (reduction of mean oral clearance by 24–37%) [25] and thiotepa IV (20% lower tepa exposure) [22]. In addition, ifosfamide clearance was increased by approximately 60% in the presence of aprepitant [23].

Non-antineoplastic drugs. Twenty publications evaluated aprepitant or fosaprepitant interactions with 16 non-antineoplastic drugs [9, 11, 35–52]. Interactions between fosaprepitant and dexamethasone PO [11] or midazolam PO [11] and between aprepitant and dexamethasone PO [44], methylprednisolone IV [44], midazolam PO/IV [9, 47, 49], oxycodone PO [39] and tolbutamide PO [46] met criteria for clinical significance.

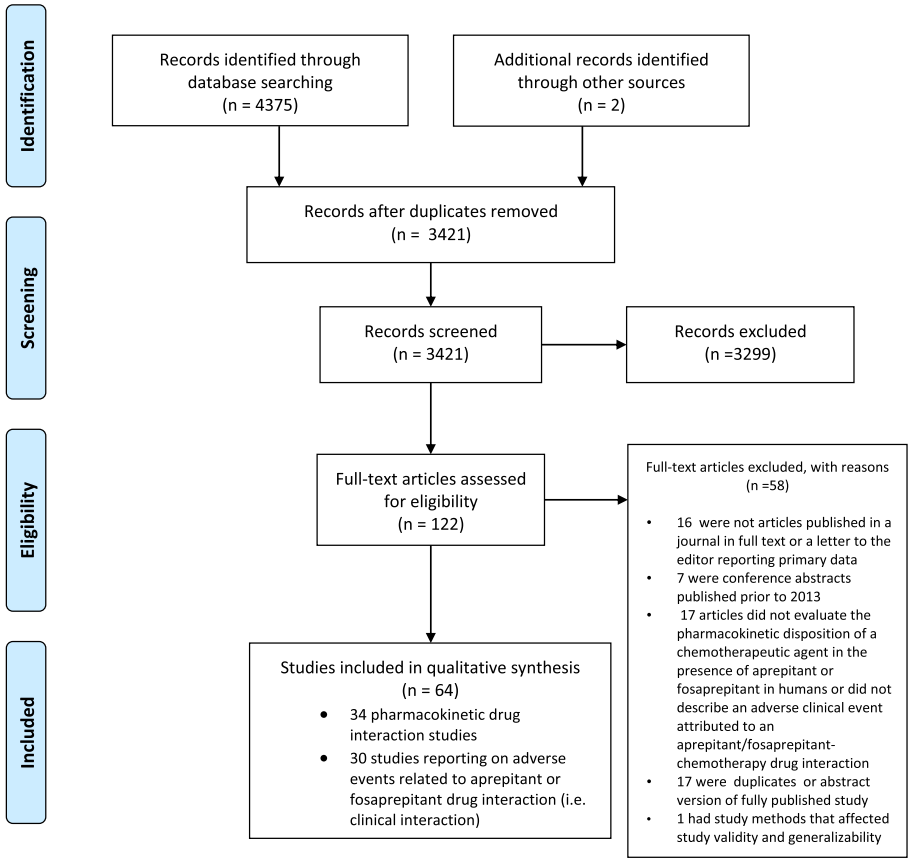

Figure 1
Study identification flow diagram

Multiple included publications evaluated aprepitant drug interactions with CYP probe drugs: midazolam PO/IV [9, 43, 47, 49] and tolbutamide PO [46, 47], implying effects on CYP3A4 and CYP2C9, respectively. A significant interaction with a higher dose of aprepitant (125 mg on day 1) was consistently demonstrated [9, 43, 47, 49]. When a lower dose of aprepitant of 40 mg PO day 1, followed by 25 mg PO on days 2 and 3 was administered with midazolam PO, the interaction did not meet criteria for clinical significance (GMR AUC_{0-inf} 1.22; 95% CI: 0.93–1.61 on day 1) [9]. Similarly, when a lower aprepitant dose of 40 mg was administered with tolbutamide PO, the interaction did not meet criteria for significance (GMR AUC_{0-inf} 0.87, 90% CI: not reported on day 4) [46].

Study authors did not report a GMR for AUC or C_{max} when describing the co-administration of the following drugs with aprepitant: alcohol IV [51], dexamethasone IV [45, 50], prednisolone PO [42], quetiapine PO [52], tacrolimus IV [40] and paroxetine PO [35]. However, significant differences in other pharmacokinetic parameters were reported when aprepitant was co-administered with several of these drugs. Reduced clearance or measures indicative of reduced clearance were observed for victim drugs which are CYP3A4 substrates: dexamethasone IV (reduction of dexamethasone clearance by approximately 25% and 50% in presence of aprepitant 40 mg or 125 mg, respectively [45, 50]), quetiapine PO (11-fold increase in plasma quetiapine concentration in presence of aprepitant [52]) and tacrolimus IV (43% increase in mean dose-normalized tacrolimus concentration in presence of aprepitant [40]). In addition, the arithmetic mean AUC_{0-24h} and C_{max} of paroxetine, a CYP2D6 substrate, were reduced by approximately 25% and 20%, respectively, in the presence of aprepitant [35].

Adverse events ascribed to interactions with aprepitant or fosaprepitant

Most (76%; 26/34) publications reporting pharmacokinetic data did not report adverse events attributed to an aprepitant/fosaprepitant drug interaction. Eight publications did report that certain adverse events occurred more frequently with concomitant aprepitant administration. Of these, only one provided *P*-values [51] and two were case reports [23, 52]. The results of these three publications are presented with the other publications evaluating adverse events attributed to aprepitant or fosaprepitant below.

Antineoplastic drugs. Twenty-four included publications reported adverse events attributed to co-administration of aprepitant or fosaprepitant and an antineoplastic agent (anthracyclines, bexarotene PO, dinaciclib IV, erlotinib, ifosfamide IV, and pazopanib IV) [23, 25, 33, 53–70, 72]. Of these, interactions between fosaprepitant and anthracyclines and aprepitant and ifosfamide IV were the suspected cause.

Table 1

Study characteristics of included studies

Article (First author, year)	Study design	*N*	Population	Median age (range), years	Aprepitant (A) or Fosaprepitant (F)	Victim drug
Pharmacokinetic drug interaction publications						
Antineoplastic drugs						
Hsyu (2015) [34]	Crossover RCT	18	Healthy	NR	A	Bosutinib PO
Sarantopoulos (2014) [30]	Crossover study	12	Solid malignancy	56 (32–71)	A	Cabazitaxel IV
Walko (2012) [32]	Crossover RCT	18	Breast cancer	55 (38–77)	A	Cyclophosphamide IV
Bubalo (2012) [21]	Parallel RCT	22	Patients scheduled for HSCT	46 (19–63)[a]	A	Cyclophosphamide IV
De Jonge (2005) [22]	PK study with historical control	8	Breast cancer or germ cell cancer	NR	A	Cyclophosphamide IV Thiotepa IV
Zhang (2012) [33]	Crossover RCT	12	Advanced malignancy	52 (35–70)	A	Dinaciclib IV
Kaneta (2014) [26]	Crossover study	16	Solid tumour	67.5 (56–76)	A	Docetaxel IV
Nygren (2005) [29]	Crossover RCT	10	Solid malignancy	NR (50–68)	A	Docetaxel IV
Mir (2011) [28]	Case report	1	Adenocarcinoma	54	A	Erlotinib (route NR)
Durand (2007) [23]	Case report	1	Metastatic osteosarcoma	57	A	Ifosfamide IV
Vadhan-Raj (2015) [31]	Crossover RCT	47	Malignancy	NR	F	Ifosfamide (route NR)
Imbs (2016) [25]	Crossover study	32	Solid malignancy	56 (24–72)	A	Pazopanib PO
Loos (2007) [27]	Crossover study	12	Advanced solid malignancy	56 (NR)	A	Vinorelbine IV
Egerer (2010) [24]	PK sub-study of parallel RCT	30	Multiple myeloma	Aprepitant arm: 57.4 (40–69)[a] Placebo arm: 62.1 (39–71)[a]	A	Melphalan IV
Non-antineoplastic drugs						
McCrea (2003) [44]	Crossover RCT	G1: 20 G2: 10	Healthy	G1: 34 (20–46)[a] G2: 31 (20–44)[a]	A	G1: Dexamethasone PO G2: Methylprednisolone IV
Marbury (2011) [11]	Crossover RCT	G1: 13 G2: 10	Healthy	Dexamethasone arm: 29.7 (18–45)[a] Midazolam: 30.1 (18–44)[a]	F	G1: Dexamethasone PO G2: Midazolam PO
Nakade (2008) [45]	PK modelling study	755	Japanese healthy patients and patients with solid malignancy	No dexamethasone: 62 (20–80) Dexamethasone arm: 63 (23–80)	A	Dexamethasone IV
Takahashi (2011) [50]	Parallel RCT	20	Japanese cancer patients receiving chemotherapy	Aprepitant 125/80/80: 59.7 (47–71)[a] Aprepitant 40/25/25: 63.6 (55–72)[a]	A	Dexamethasone IV
Blum (2003) [36]	Crossover RCT	G1: 17 G2: 15	Healthy	G1: 27.9 (18–44)[a] G2: 34.4 (19–46)[a]	A	G1: Granisetron PO G2: Ondansetron IV
Li (2006) [41]	Crossover RCT	12	Healthy	NR (19–52)	A	Dolasetron PO
Majumdar (2003) [9]	Crossover RCT	16	Healthy	30 (20–43)[a]	A	Midazolam PO

(*continues*)

Table 1

(Continued)

Article (First author, year)	Study design	*N*	Population	Median age (range), years	Aprepitant (A) or Fosaprepitant (F)	Victim drug
Shadle (2004) [47]	Parallel RCT	24	Healthy	Aprepitant: 29 (18–40)[a] Placebo: 29 (21–44)[a]	A	Midazolam IV Tolbutamide PO
Majumdar (2007) [43]	Crossover RCT	12	Healthy	NR (20–36)	A	Midazolam IV
Stoch (2011) [49]	Crossover study	12	Healthy	34 (22–44)[a]	A	Midazolam PO and IV
Fujiwara (2014) [39]	Crossover study	20	Stage IV cancer	66.5 (44–77)	A	Oxycodone PO
Shah (2005) [48]	Crossover RCT	12	Healthy	29.9 (NR)[a]	A	Palonosetron IV
Maie (2014) [42]	Crossover study	8	Lymphoma	NR	A	Prednisolone PO
Verwimp-Hoeks (2012) [52]	Case report	1	Laryngeal carcinoma + depression + anxiety	44	A	Quetiapine PO
Ibrahim (2008) [40]	Retrospective review	26	Reduced intensity HSCT patients	52.5 (18–68)	A	Tacrolimus IV
Ngo (2009) [46]	Parallel RCT	22	Healthy	Aprepitant: 27 (19–37) Placebo: 26 (19–39)	A	Tolbutamide PO
Depre (2005) [37]	Parallel RCT	22	Healthy	29 (21–45)[a]	A	Warfarin PO
Feuring (2003) [38]	Crossover RCT	11	Healthy	29.6 (22–45)[a]	A	Digoxin PO
Ball (2014) [35]	Parallel RCT	236	Major depressive disorder	38.9 (18–65)	A	Paroxetine PO
te Beek (2013) [51]	Crossover RCT	17	Healthy	27 (18–53)[a]	A	Alcohol IV
Clinical drug interaction publications (i.e. publications that did not report pharmacokinetic data)						
Antineoplastic drugs						
Kameda (2014) [60]	Prospective observational cohort study	20	Japanese, breast cancer	48.5 (23–67)[b]	F	Anthracycline IV
Sato (2014) [64]	Retrospective review	56	Receiving fosaprepitant through peripheral IV line	50 (31–85)	F	Anthracycline IV
Lundberg (2014) [61]	Retrospective review	150	Patients administered fosaprepitant IV through a peripheral vein	Reaction group: 54 (IQR: 49–62) No reaction group: 59 (IQR: 51–67)	F	Anthracycline IV
Mogi (2014) [62]	Retrospective review	80	Colorectal cancer	NR	F	Anthracycline IV
Fujii (2015) [55]	Retrospective study	267	Patients administered anthracycline or cisplatin based regimen *not* through a central line	54.3 (NR)[a]	A/F	Anthracycline/ Platinum IV
Hegerova (2015) [56]	Retrospective review	180	Patients administered platinum-based therapy not containing anthracycline or patients administered anthracycline-cyclophosphamide hemotherapy	Platinum-based chemotherapy: 46.4 (22–77)[a] Anthracycline-based chemotherapy: 53.3 (31–74)[a]	F	Anthracycline/ Platinum IV

(*continues*)

Table 1

(Continued)

Article (First author, year)	Study design	*N*	Population	Median age (range), years	Aprepitant (A) or Fosaprepitant (F)	Victim drug
Tsuda (2016) [73]	Retrospective review	100	Chemo-naïve breast cancer patients receiving anthracycline-containing chemotherapy	Aprepitant: 52 (30–75) Fosaprepitant: 47 (31–66)	A/F	Anthracycline IV
Ruellan (2012) [63]	Case report	1	Erthyrodermic Sezary syndrome	65	A	Bexarotene PO
Sassier (2016) [71]	Case report	1	Non-small cell lung cancer and brain metastases	56	A	Erlotinib (route NR)
Howell (2008) [58]	Retrospective cohort study	45	Sarcoma	Aprepitant: 53 (NR)[a] No aprepitant: 48 (NR)[a]	A	Ifosfamide IV
Ho (2010) [57]	Retrospective case–control	54	Sarcoma	Cases: 48 (NR)[a] Controls: 44.8 (NR)[a]	A	Ifosfamide IV
Stern (2015) [67]	Retrospective study	187	Treated with ifosfamide	27 (0–78)	A	Ifosfamide IV
Chenaf (2015) [54]	Retrospective review of pharmacovigilance database	178	Treated with ifosfamide and experiencing neurotoxicity	Brand name: 49 (NR) Generic: 14 (NR)	A	Ifosfamide (route NR)
Gupta (2016) [69]	Retrospective chart review	81	Treated with ifosfamide	NR	F	Ifosfamide IV
Mahe (2016) [70]	Retrospective study	213	Treated with ifosfamide	13 (1–20)[c]	A	Ifosfamide (route NR)
Jarkowski (2008) [59]	Case report	1	Malignant peripheral nerve sheath tumour	24	A	Ifosfamide IV
McDonnell (2012) [68]	Case report	1	Non-Hodgkin lymphoma	66	A	Ifosfamide (route NR)
Shindorf (2013) [66]	Case reports	2	C1: Ovarian malignant mixed mesodermal tumour (MMMT), C2: uterine MMMT	C1: 67C2: 41	A	Ifosfamide IV
Sejourne (2014) [65]	Case reports	2	C1: uterine leiomyosarcoma C2: pleiomorphic rhabdomyosarcoma	C1: 39 C2: 75	A	Ifosfamide IV
Barthelemi (2015) [53]	Case series	10	Ifosfamide-induced encephalopathy	NR (8 children: 2–15; 2 adults: 51 and 80)	A	Ifosfamide (route NR)
Sunela (2016) [72]	Case reports	2	C1: osteosarcoma with previous history of breast cancer C2: metastatic sarcoma	C1: 59 C2: 65	A	Ifosfamide IV
Non-antineoplastic drugs						
Walsh (2013) [78]	Crossover RCT	8	Illicit opioid users	32.3 (NR)[a]	A	Oxycodone intranasal and PO
Jones (2013) [74]	Parallel RCT	15	Methadone-maintained patients with opioid abuse and dependence	47.3 (31–59)[a]	A	Methadone PO
Mir (2012) [75]	Retrospective case–control study	44	Chemotherapy naïve patients receiving SSRI or SNRI	59 (34–78)	A	SSRI (route NR)

(*continues*)

Table 1

(Continued)

Article (First author, year)	Study design	*N*	Population	Median age (range), years	Aprepitant (A) or Fosaprepitant (F)	Victim drug
Takaki (2016) [82]	Retrospective study	14	Patients receiving anticancer therapy	59 (33–78)[a]	A	Warfarin PO
Yano (2011) [79]	Case reports	2	C1: ovarian malignancy + disseminated intravascular coagulation	C1: 50	A	Warfarin PO
			C2: peritoneal recurrence and liver metastasis of uterine cervical adenocarcinoma	C2: 43		
Ohno (2014) [77]	Case reports	2	C1: small cell lung cancer + atrial fibrillation, Japanese	C1: 60	A	Warfarin PO
			C2: endometrial carcinoma + pulmonary thrombosis and deep vein thrombosis, Japanese	C2: 47		
Nakano (2015) [76]	Case report	1	Squamous cell carcinoma including urothelial carcinoma + deep vein thrombosis	64	A	Warfarin PO
Inagaki (2015) [80]	Case report	1	Clear cell carcinoma + pulmonary embolism	63	A	Warfarin (route NR)
Okada (2016) [81]	Case report	1	Rhabdomyosarcoma and occlusion of left middle cerebral artery, Japanese	15	A	Warfarin PO

RCT, randomized controlled trial; NR, not reported; PK, pharmacokinetic; IQR, interquartile range; C1: case 1, C2: case 2; G1: group 1; G2: group 2; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor

[a]Mean age and range reported

[b]Characteristics of 6 patients who experienced vascular-pain only presented by study authors

[c]Patients who experienced neurotoxicity

Table 2

Summary of findings regarding pharmacokinetic interactions with aprepitant/fosaprepitant

Drugs evaluated for pharmacokinetic interactions with aprepitant		
Clinically significant interaction[a]:	Antineoplastic agents:	bosutinib PO cabazitaxel IV cyclophosphamide IV
	Non-antineoplastic agents:	dexamethasone PO methylprednisolone IV midazolam IV and PO oxycodone PO tolbutamide PO
Possibly significant interaction[b]:	Antineoplastic agents:	erlotinib (route not reported) ifosfamide IV pazopanib PO thiotepa IV
	Non-antineoplastic agents:	dexamethasone IV paroxetine PO quetiapine PO tacrolimus IV
Possibly no clinically significant interaction[c]:	Antineoplastic agents:	melphalan IV
	Non-antineoplastic agents:	alcohol IV prednisolone PO
No clinically significant interaction[d]:	Antineoplastic agents:	dinaciclib IV docetaxel IV vinorelbine IV
	Non-antineoplastic agents:	digoxin PO dolasetron PO granisetron PO ondansetron IV palonosetron IV warfarin PO
Drugs evaluated for pharmacokinetic interactions with fosaprepitant		
Clinically significant interaction[a]:	Antineoplastic agents:	none evaluated
	Non-antineoplastic agents:	dexamethasone PO midazolam PO
No clinically significant interaction[c]:	Antineoplastic agents:	ifosfamide IV
	Non-antineoplastic agents:	none evaluated

[a]Met pre-defined definition of clinical significance;
[b]Significant change in pharmacokinetic parameters observed; GMR of C_{max} or AUC not provided;
[c]No significant change in pharmacokinetic parameters observed; GMR of C_{max} or AUC not provided;
[d]Did not meet pre-defined definition of clinical significance

One prospective study [60] and six retrospective studies [55, 56, 61, 62, 64, 73] evaluated the incidence of phlebitis when fosaprepitant and anthracycline chemotherapy were administered *via* the same peripheral vein. Two of these studies compared the incidence of this adverse event in patients receiving anthracycline *vs.* non-anthracycline chemotherapy [55, 56]. In these studies, the reported odds ratios of having phlebitis with fosaprepitant and anthracycline therapy *vs.* fosaprepitant and platinum chemotherapy were 12.95 (95% CI: 5.74 to 29.2) [55] and 8.1 (95% CI: 2.0 to 31.9) [56]. Other studies comparing phlebitis rates with/without fosaprepitant also noted statistically significant increases in phlebitis with fosaprepitant compared to aprepitant [62, 64, 73].

Thirteen publications (six retrospective studies, nine case reports and one case series) [23, 53, 54, 57–59, 65–70, 72] evaluated neurotoxicity associated with the combination of ifosfamide and aprepitant/fosaprepitant. The interaction between aprepitant and ifosfamide was a probable cause of neurotoxicity in one of the nine case reports (DIPS: 6) [23]. Neurotoxicity was unlikely to be due to an interaction between ifosfamide and aprepitant/fosaprepitant in the remaining case reports (DIPS: <5) [59, 65, 66, 68, 72]. Results from the retrospective studies, four specifically evaluating the co-administration of ifosfamide IV with aprepitant/fosaprepitant [57, 58, 69, 70] and two evaluating general risk factors for ifosfamide-induced neurotoxicity [54, 67], did not demonstrate an increased likelihood of ifosfamide-induced neurotoxicity or encephalopathy in the presence of aprepitant/fosaprepitant.

Non-antineoplastic drugs. Fourteen included studies [35, 43, 46, 51, 52, 74–82] described potential drug interactions between aprepitant and alcohol IV, methadone PO,

midazolam IV, oxycodone intranasal and PO, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors PO (SSRIs/SNRIs), paroxetine PO, quetiapine PO, tolbutamide PO, and warfarin PO. A probable interaction was observed between aprepitant and alcohol IV [51], oxycodone [78], quetiapine PO [52], SSRIs/SNRIs [75] and warfarin [76, 77, 79, 82].

A randomized crossover study evaluating the pharmacokinetics of alcohol IV with/without aprepitant also conducted psychomotor and cognitive function tests on its subjects. A statistically significant decline in function was found for immediate pattern recognition (P = 0.043) and adaptive tracking at 7.5 h (P = 0.043) when aprepitant was given concomitantly with alcohol IV. However, study authors concluded that these differences were not clinically relevant [51].

A randomized crossover study examined the effects of aprepitant on the subjective and physiologic response to oxycodone in individuals with opioid abuse to identify whether neurokinin-1 receptor antagonists diminish the effects of opioids related to their abuse potential [78]. A statistically significant enhanced response to high oxycodone doses was noted in the presence of aprepitant with aprepitant increasing the 'high' that patients experienced (PO oxycodone: P = 0.39; intranasal oxycodone: P = 0.007) and the estimated street value of the oxycodone (PO oxycodone: P = 0.023; intranasal oxycodone: P = 0.004). A lower respiratory rate (PO oxycodone: $P < 0.025$; intranasal oxycodone: 0.005) and increased end tidal carbon dioxide (PO oxycodone: P = 0.028; intranasal oxycodone: P = 0.001) was also noted in the presence of aprepitant.

A case report suggested a probable interaction between quetiapine PO and aprepitant (DIPS: 6). Deep somnolence was reported when aprepitant was administered with quetiapine on days the patient was receiving chemotherapy [52].

In addition, a retrospective, case–control study found that patients receiving aprepitant together with SSRIs/SNRIs PO had higher rates of National Cancer Institute-Common Toxicity Criteria version 3.0 (NCI-CTC v3.0) grade 2 or greater vomiting than a patient not receiving a SSRI or SNRI (P = 0.04) [75].

One retrospective study and seven case reports described changes to International Normalized Ratio (INR) following the initiation of aprepitant administration in patients receiving chronic warfarin therapy [76, 77, 79–82]. The retrospective study reported statistically significant increases in INR during the first week after aprepitant administration (P = 0.0000149) and significant decreases 2 weeks after aprepitant administration (P = 0.00069) *vs*. the week prior to aprepitant administration. The DIPS scores for four of these case reports indicated that an interaction between aprepitant and warfarin PO was probable [76, 77, 79].

Discussion

Interactions between aprepitant/fosaprepitant and bosutinib PO [34], cabazitaxel IV [30], cyclophosphamide IV [32], dexamethasone PO [11, 44], methylprednisolone IV [44], midazolam PO/IV [9, 43, 47, 49], oxycodone PO [39] and tolbutamide PO [47] were clinically significant as defined by the FDA [17]. In addition, clinical descriptions of adverse events probably or highly probably caused by co-administration of aprepitant or fosaprepitant with alcohol IV [51], anthracyclines IV [55, 56, 60–62, 64, 73], ifosfamide IV [23], midazolam IV [43], oxycodone intranasal and PO [78], quetiapine PO [52], SSRIs/SNRIs [75] and warfarin PO [76, 77, 79, 82] were identified.

Midazolam and tolbutamide are commonly used as probes in drug interaction studies to determine whether the investigated drug is an inhibitor or inducer of CYP3A4 or CYP2C9, respectively [17]. Included publications using midazolam PO support the classification of fosaprepitant as a weak CYP3A4 inhibitor [11] and aprepitant as a moderate CYP3A4 inhibitor [9] after the administration of the usual adult doses for CINV prevention. Delayed effects of aprepitant as a weak CYP3A4 inducer [47, 49] and a weak CYP2C9 inducer have also been noted several days after the administration of aprepitant [47].

Interestingly, the information required to apply the FDA definition of a significant interaction was not provided in 40% (14/35) of included pharmacokinetic studies. However, in 10 of these 14 publications, significant differences in pharmacokinetic parameters other than GMR for C_{max} or AUC were reported for the following victim drugs: dexamethasone IV, erlotinib (route not reported), ifosfamide IV, quetiapine PO, pazopanib PO, paroxetine PO, tacrolimus IV and thiotepa IV [22, 23, 25, 28, 35, 40, 45, 50, 52]. Hence, there is a possibility that these interactions may be clinically significant and caution is advisable when these drugs are administered with aprepitant.

In several instances (e.g. dinaciclib IV, ifosfamide, vinorelbine IV, dolasetron PO (poor metabolizers), granisetron PO, ondansetron IV and palonosetron IV), considerable variability in the GMR was observed and the upper or lower limit of the 90% CI exceeded the GMR threshold for clinical significance [27, 31, 33]. The FDA guidance document states that a drug interaction can be considered not to be clinically significant if the 90% CI for the systemic exposure ratios fall completely within 80 to 125% [17]. Thus, cases where the 90% CIs for the GMR for AUC or C_{max} fall outside this range may be a cause for concern.

Cyclophosphamide IV merits discussion since pharmacokinetic data were not reported consistently across the three included publications that describe the co-administration of aprepitant and cyclophosphamide [21, 22, 32]. One of these three publications reported GMRs for AUC and C_{max} with/without aprepitant and a designation of a clinically significant interaction was made based on this information [32]. Study authors for the other two publications did not report a clinically significant interaction. However, specific AUC and C_{max} values were not reported in either of these publications and we were unable to draw conclusions based on our predefined definition [21, 22].

Reports of the interaction between ifosfamide and aprepitant/fosaprepitant were also conflicting. While case reports [23, 59, 65, 66, 72] attributed ifosfamide-induced neurotoxicity to an aprepitant-ifosfamide drug interaction, only one case report had a DIPS score that would suggest that the interaction was the probable cause (DIPS score: 6) [23]. The included retrospective studies did not report P-values or

demonstrate a statistically significant difference in ifosfamide-induced neurotoxicity rates in the presence of aprepitant [54, 57, 58, 67, 69, 70]. Furthermore, results from a randomized crossover trial reported GMRs for C_{max} and AUC with/without fosaprepitant that did not meet our definition of a clinically significant interaction [31]. Large, prospective studies are required to determine risk factors, including the co-administration of aprepitant or fosaprepitant, for ifosfamide-induced neurotoxicity.

All of the victim drugs that were found to have a clinically significant pharmacokinetic interaction with aprepitant or fosaprepitant were CYP3A4 or CYP2C9 substrates, consistent with what is known about the pharmacology of aprepitant and fosaprepitant. However, several CYP3A4 or CYP2C9 substrates were found not to interact to a clinically significant extent with aprepitant or fosaprepitant. Co-administration of aprepitant and CYP3A4 substrates which were also substrates of p-glycoprotein or other efflux transporters (Supporting Information Appendix S4) often did not lead to significant changes in pharmacokinetic disposition. We speculate that, for these drugs, elimination *via* alternative pathways compensates for inhibition of CYP3A4 by aprepitant/fosaprepitant and mitigates the magnitude of the interaction.

Patient-related factors may also influence the magnitude of a CYP3A4-mediated drug interaction. Patients with increased sensitivity to CYP3A4 inhibition or with reduced capacity to compensate for CYP3A4 inhibition may be at higher risk of clinically significant interactions with aprepitant or fosaprepitant. For example, patients may have reduced CYP3A4 and hepatic drug transporter activity by virtue of their age, disease states, genotype or concurrent drug therapy. Patients with inflammatory conditions or cancer may also have reduced CYP3A4 capacity [83]. Young children may be particularly vulnerable since CYP3A4 concentrations steadily increase after birth and reach 30–40% of adult levels during the first year of life [84]. Similarly, the activities of potentially compensatory pathways such as hepatic drug transporters p-glycoprotein and organic anion-transporting polypeptide transporters increase with age [85].

The strength of this systematic review is its rigorous approach to identify drug interaction publications, its application of a well-recognized definition of clinical significance of drug interactions and its use of a validated tool to assess the probability of adverse events described in case reports.

It is limited by the small sample size of many of the included studies and lack of power to detect differences in adverse events, as well as, at least for the non-antineoplastic victim medications, the conduct of many studies in healthy subjects. This limits the external generalizability of study results and was reflected in the quality assessment of included studies. Our ability to assess the clinical significance of pharmacokinetic interactions was also limited by the proportion of reports which did not present values for GMR for AUC or C_{max}. With respect to the drug interaction studies reporting adverse events, an association between the reported adverse event and co-administration of aprepitant and a victim drug could not always be confirmed as a result of multiple confounding factors. For example, many of the studies evaluating ifosfamide-induced neurotoxicity were confounded by the presence of other potential risk factors, such as plasma albumin concentrations and co-administration of central nervous system acting agents. This ambiguity is reflected in the DIPS scores. Furthermore, the evaluation of adverse events related to drug interactions was limited to the timeframe of the studies. It is possible that changes in exposure to chemotherapy may have long-term consequences. No publication was identified that evaluated the long-term effects of an aprepitant/fosaprepitant drug interaction. This is an evidence gap that requires further investigation.

Despite these limitations, the findings of this systematic review are generalizable to adults with cancer since most studies (27/34) evaluated drug interactions after a single 125 mg dose of aprepitant or when given at the FDA-approved adult dose (Supplemental Tables S6–S9). The findings are also generalizable to most children since CYP3A4 activity approaches adult levels by early childhood.

Conclusion

Using systematic methods, we identified clinically significant interactions between aprepitant and fosaprepitant and 14 drugs. Administration of fosaprepitant and anthracycline antineoplastic agents *via* the same peripheral vein should be avoided. Dose adjustment of the victim drug or use of antiemetic agents other than aprepitant or fosaprepitant should be considered for patients receiving dexamethasone PO, methylprednisolone IV, midazolam PO/IV, oxycodone PO, or tolbutamide PO. We suggest that neurokinin-1 receptor antagonists without CYP3A4 activity be considered for patients receiving bosutinib PO, cabazitaxel IV or cyclophosphamide IV. Although less clear, the use of antiemetics other than aprepitant/fosaprepitant may be appropriate in patients receiving erlotinib, pazopanib IV or thiotepa IV. Our findings are summarized in Table 2. Individuals with reduced capacity to metabolize drugs *via* CYP3A4 or other pathways, including neonates and young children, may be at higher risk of experiencing clinically significant interactions due to aprepitant/fosaprepitant drug co-administration.

Competing Interests

There are no competing interests to declare.

We thank Ms. Alanna Marson and Ms. Joanna Bielecki for guidance with the search strategy for the systematic review. We would also like to thank Dr. Lusine Abrahamyan and Dr. Petros Pechlivanoglou for support and guidance. We are grateful to Dr. Masanobu Takeuchi and Dr. Hitomi Hino for their help with article translation.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Alexander SPH, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: G protein coupled receptors. Br J Pharmacol 2015; 172: 5744–869.

3 Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

4 Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, *et al*., American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011; 29: 4189–98.

5 Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, *et al*., Group EMGW. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 2010; 21 (Suppl 5): v232–43.

6 Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, *et al*., Pediatric Oncology Group of Ontario. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer 2013; 60: 1073–82.

7 Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. Lancet Oncol 2015; 16: 385–94.

8 Merck Canada Inc. Product Monograph Emend. Health Canada Drug Product Database. Available at https://health-products.canada.ca/dpd-bdpp/info.do?code=78411&lang=en (last accessed 10 October 2016).

9 Majumdar AK, McCrea JB, Panebianco DL, Hesney M, Dru J, Constanzer M, *et al*. Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. Clin Pharmacol Ther 2003; 74: 150–6.

10 Merck Canada Inc. Product Monograph Emend IV. Health Canada Drug Product Database. Available at https://health-products.canada.ca/dpd-bdpp/info.do?code=84835&lang=en (last accessed 10 October 2016).

11 Marbury TC, Ngo PL, Shadle CR, Jin B, Panebianco D, Caro L, *et al*. Pharmacokinetics of oral dexamethasone and midazolam when administered with single-dose intravenous 150 mg fosaprepitant in healthy adult subjects. J Clin Pharmacol 2011; 51: 1712–20.

12 U.S. Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. Available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (last accessed 11 October 2016).

13 Hansten P, Horn J. Drug–drug interaction mechanisms. H&H Publications. Available at http://www.hanstenandhorn.com/article-d-i.html (last accessed 11 October 2016).

14 MASCC, Multinational Association for Supportive Care in Cancer™. MASCC/ESMO Antiemetic Guidelines, 2016. Available at http://www.mascc.org/antiemetic-guidelines (last accessed 11 October 2016).

15 Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*., The PRSIMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647.

16 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6: e1000100.

17 U.S. Food and Drug Administration. Drug interaction studies – study design, data analysis, implications for dosing, and labeling recommendations. Available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093606.htm (last accessed 11 October 2016).

18 Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother 2007; 41: 674–80.

19 Shayani S, Palmer JM, Stiller T, Chan H, Keuylian S, Parker P, *et al*. Aprepitant (Emend) significantly increases sirolimus levels in patients undergoing allogeneic hematopoietic SCT. Bone Marrow Transplant 2012; 47: 291–3.

20 McHugh ML. Interrater reliability: the kappa statistic. Biochem Med 2012; 22: 276–82.

21 Bubalo JS, Cherala G, McCune JS, Munar MY, Tse S, Maziarz R. Aprepitant pharmacokinetics and assessing the impact of aprepitant on cyclophosphamide metabolism in cancer patients undergoing hematopoietic stem cell transplantation. J Clin Pharmacol 2012; 52: 586–94.

22 De Jonge ME, Huitema ADR, Holtkamp MJ, Van Dam SM, Beijnen JH, Rodenhuis S. Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism. Cancer Chemother Pharmacol 2005; 56: 370–8.

23 Durand JP, Gourmel B, Mir O, Goldwasser F. Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. Ann Oncol 2007; 18: 808–9.

24 Egerer G, Eisenlohr K, Gronkowski M, Burhenne J, Riedel KD, Mikus G. The NK receptor antagonist aprepitant does not alter the pharmacokinetics of high-dose melphalan chemotherapy in patients with multiple myeloma. Br J Clin Pharmacol 2010; 70: 903–7.

25 Imbs DC, Dieras V, Bachelot T, Campone M, Isambert N, Joly F, *et al*. Pharmacokinetic interaction between pazopanib and cisplatin regimen. Cancer Chemother Pharmacol 2016; 77: 385–92.

26 Kaneta T, Fujita KI, Akiyama Y, Kawara K, Sunakawa Y, Kawachi A, *et al*. No pharmacokinetic alteration of docetaxel following coadministration of aprepitant 3 h before docetaxel infusion. Cancer Chemother Pharmacol 2014; 74: 539–47.

27 Loos WJ, De Wit R, Freedman SJ, Van Dyck K, Gambale JJ, Li S, *et al*. Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. Cancer Chemother Pharmacol 2007; 59: 407–12.

28 Mir O, Blanchet B, Goldwasser F. More on aprepitant for erlotinib-induced pruritus. N Engl J Med 2011; 364: 487.

29 Nygren P, Hande K, Petty KJ, Fedgchin M, Van Dyck K, Majumdar A, *et al*. Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. Cancer Chemother Pharmacol 2005; 55: 609–16.

30 Sarantopoulos J, Mita AC, Wade JL, Morris JC, Rixe O, Mita MM, *et al*. Phase I study of cabazitaxel plus cisplatin in patients with advanced solid tumors: study to evaluate the impact of cytochrome P450 3A inhibitors (aprepitant, ketoconazole) or

inducers (rifampin) on the pharmacokinetics of cabazitaxel. Cancer Chemother Pharmacol 2014; 74: 1113–24.

31 Vadhan-Raj S, Zhou X, Spasojevic I, Ravi V, Araujo D, Somaiah N, *et al*. Randomised, cross over study of fosaprepitant (single dose *vs*. two doses) for nausea and vomiting in sarcoma patients receiving multi-day chemotherapy. Support Care Cancer 2015; 1: S131–2.

32 Walko CM, Combest AJ, Spasojevic I, Yu AYC, Bhushan S, Hull JH, *et al*. The effect of aprepitant and race on the pharmacokinetics of cyclophosphamide in breast cancer patients. Cancer Chemother Pharmacol 2012; 69: 1189–96.

33 Zhang D, Mita M, Shapiro GI, Poon J, Small K, Tzontcheva A, *et al*. Effect of aprepitant on the pharmacokinetics of the cyclin-dependent kinase inhibitor dinaciclib in patients with advanced malignancies. Cancer Chemother Pharmacol 2012; 70: 891–8.

34 Hsyu PH, Matschke K, Soriano-Pignataro D. An open-label, randomized, 2-period crossover study to evaluate the effect of a single oral dose of aprepitant, a moderate CYP3A inhibitor on bosutinib administered orally to healthy subjects. In: 2015 AAPS Annual Meeting and Exposition, Orlando, FL, USA.

35 Ball WA, Snavely DB, Hargreaves RJ, Szegedi A, Lines C, Reines SA. Addition of an NK1 receptor antagonist to an SSRI did not enhance the antidepressant effects of SSRI monotherapy: results from a randomized clinical trial in patients with major depressive disorder. Hum Psychopharmacol 2014; 29: 568–77.

36 Blum RA, Majumdar A, McCrea J, Busillo J, Orlowski LH, Panebianco D, *et al*. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. Clin Ther 2003; 25: 1407–19.

37 Depre M, Van Hecken A, Oeyen M, De Lepeleire I, Laethem T, Rothenberg P, *et al*. Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. Eur J Clin Pharmacol 2005; 61: 341–6.

38 Feuring M, Lee Y, Orlowski LH, Michiels N, De Smet M, Majumdar AK, *et al*. Lack of effect of aprepitant on digoxin pharmacokinetics in healthy subjects. J Clin Pharmacol 2003; 43: 912–7.

39 Fujiwara Y, Toyoda M, Chayahara N, Kiyota N, Shimada T, Imamura Y, *et al*. Effects of aprepitant on the pharmacokinetics of controlled-release oral oxycodone in cancer patients. PLoS One 2014; 9: e104215.

40 Ibrahim RB, Abidi MH, Ayash LJ, Cronin SM, Cadotte C, Mulawa J, *et al*. Effect of aprepitant on intravenous tacrolimus disposition in reduced intensity hematopoietic stem cell transplantation. [Erratum appears in J Oncol Pharm Pract. 2008 Dec; 14(4): 233]. J Oncol Pharm Pract 2008; 14: 113–21.

41 Li SX, Pequignot E, Panebianco D, Lupinacci P, Majumdar A, Rosen L, *et al*. Lack of effect of aprepitant on hydrodolasetron pharmacokinetics in CYP2D6 extensive and poor metabolizers. J Clin Pharmacol 2006; 46: 792–801.

42 Maie K, Okoshi Y, Takaiwa N, Kurita N, Hasegawa Y, Homma M, *et al*. Aprepitant does not alter prednisolone pharmacokinetics in patients treated with R-CHOP. Ann Oncol 2014; 25: 298–9.

43 Majumdar AK, Yan KX, Selverian DV, Barlas S, Constanzer M, Dru J, *et al*. Effect of aprepitant on the pharmacokinetics of intravenous midazolam. J Clin Pharmacol 2007; 47: 744–50.

44 McCrea JB, Majumdar AK, Goldberg MR, Iwamoto M, Gargano C, Panebianco DL, *et al*. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003; 74: 17–24.

45 Nakade S, Ohno T, Kitagawa J, Hashimoto Y, Katayama M, Awata H, *et al*. Population pharmacokinetics of aprepitant and dexamethasone in the prevention of chemotherapy-induced nausea and vomiting. Cancer Chemother Pharmacol 2008; 63: 75–83.

46 Ngo PL, Shadle CR, Murphy MG, Jin B, Panebianco DL, Evans JK, *et al*. Effect of aprepitant 40 mg on cytochrome P-450 2C9 activity: a randomized, double-blind, placebo-controlled, parallel-group study in healthy young adults. J Appl Res 2009; 9: 123–31.

47 Shadle CR, Lee Y, Majumdar AK, Petty KJ, Gargano C, Bradstreet TE, *et al*. Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity. J Clin Pharmacol 2004; 44: 215–23.

48 Shah AK, Hunt TL, Gallagher SC, Cullen MT Jr. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. Curr Med Res Opin 2005; 21: 595–601.

49 Stoch SA, Gargano C, Valentine J, Braun MP, Murphy MG, Fedgchin M, *et al*. Double-blind crossover study to assess potential differences in cytochrome P450 3A4 activity in healthy subjects receiving ondansetron plus dexamethasone, with and without aprepitant. Cancer Chemother Pharmacol 2011; 67: 1313–21.

50 Takahashi T, Nakamura Y, Tsuya A, Murakami H, Endo M, Yamamoto N. Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients. Cancer Chemother Pharmacol 2011; 68: 653–9.

51 te Beek ET, Tatosian D, Majumdar A, Selverian D, Klaassen ES, Petty KJ, *et al*. Placebo- and amitriptyline-controlled evaluation of central nervous system effects of the NK1 receptor antagonist aprepitant and intravenous alcohol infusion at pseudo-steady state. J Clin Pharmacol 2013; 53: 846–56.

52 Verwimp-Hoeks MPA, Van Herpen CML, Burger DM. Aprepitant quetiapine: a clinically significant drug interaction in a patient treated for head and neck cancer. Ann Oncol 2012; 23: 801–2.

53 Barthelemi L, Bara E, Descoeur J, Hillaire-Buys D, Mathieu O, Sirvent N. Ifosfamide-induced encephalopathy: symptoms and efficacy of methylene blue (MB) in the treatment and prevention of this adverse effect. Fundam Clin Pharmacol 2015; 29: 24.

54 Chenaf C, Barthelemi L, Descoeur J, Fournier-Choma C, Hillaire-Buys D, Zenut M. Ifosfamide-induced neurotoxicity, brand-name versus generic formulation: a review of the French Pharmacovigilance Database. Fundam Clin Pharmacol 2015; 29: 40.

55 Fujii T, Nishimura N, Urayama KY, Kanai H, Ishimaru H, Kawano J, *et al*. Differential impact of fosaprepitant on infusion site adverse events between cisplatin- and anthracycline-based chemotherapy regimens. Anticancer Res 2015; 35: 379–84.

56 Hegerova LT, Leal AD, Grendahl DC, Seisler DK, Sorgatz KM, Anderson KJ, *et al*. An analysis of fosaprepitant-induced venous toxicity in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2015; 23: 55–9.

57 Ho H, Yuen C. Letter to the editor. J Oncol Pharm Pract 2010; 16: 137–8.

58 Howell JE, Szabatura AH, Hatfield Seung A, Nesbit SA. Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant. J Oncol Pharm Pract 2008; 14: 157–62.

59 Jarkowski IA. Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. Am J Health Syst Pharm 2008; 65: 2229–31.

60 Kameda K, Kiba T, Ogawa Y, Kimoto S, Kajiume S, Okada Y, *et al*. Effect of dexamethasone on vascular pain caused by the administration of fosaprepitant dimeglumine and epirubicin hydrochloride in patients with primary breast cancer. Gan to kagaku ryoho [Cancer & chemotherapy] 2014; 41: 1255–7.

61 Lundberg JD, Crawford BS, Phillips G, Berger MJ, Wesolowski R. Incidence of infusion-site reactions associated with peripheral intravenous administration of fosaprepitant. Support Care Cancer 2014; 22: 1461–6.

62 Mogi A, Takamatsu Y, Fukuda M, Oda M, Kuboda T, Nishida M, *et al*. Evaluation of phlebitis attribute to chemotherapy in colorectal cancer patients of our institution. Ann Oncol 2014; 25: v67.

63 Ruellan AL, Dreno B, Saint-Jean M, Joyau C, Mahe J, Veyrac G, *et al*. Interaction between bexarotene and aprepitant: the first case of death. Drug Saf 2012; 35: 897.

64 Sato Y, Kondo M, Inagaki A, Komatsu H, Okada C, Naruse K, *et al*. Highly frequent and enhanced injection site reaction induced by peripheral venous injection of fosaprepitant in anthracycline-treated patients. J Cancer 2014; 5: 390–7.

65 Sejourne A, Noal S, Boone M, Bihan C, Sassier M, Andrejak M, *et al*. Two cases of fatal encephalopathy related to ifosfamide: an adverse role of aprepitant? Case Rep Oncol 2014; 7: 669–72.

66 Shindorf ML, Manahan KJ, Geisler JP. The interaction of ifosfamide and aprepitant in gynecologic malignancies. Gynecol Oncol Case Rep 2013; 6: 34–5.

67 Stern N, Lervat C, Defachelles AS, Ryckewaert T, Marliot G, Sakji I, *et al*. Risk factors for ifosfamide-related encephalopathy (IRE) in sarcoma (S) patients (pts). J Clin Oncol Conf 2015; 33: e21523.

68 McDonnell AM, Rybak I, Wadleigh M, Fisher DC. Suspected serotonin syndrome in a patient being treated with methylene blue for ifosfamide encephalopathy. J Oncol Pharm Pract 2012; 18: 436–9.

69 Gupta R, Hartwell R, Khanal R, Chen J, Hayes GL, Perez A, *et al*. Fosaprepitant as a risk factor for ifosfamide induced encephalopathy: a single institution experience. J Clin Oncol Conf 2016; 34: e14104.

70 Mahe J, Corradini N, Chauvin C, Joyau C, Ruellan AL, Veyrac G, *et al*. Retrospective study on determinants of ifosfamide induced neurotoxicity. Drug Saf 2015; 38: 1001.

71 Sassier M, Peyro-Saint-Paul L, Clarisse B, Leconte A, Coquerel A, Alexandre J, *et al*. Chemotherapy (platinum and pemetrexed) in combination with erlotinib in non-small cell lung cancer induces major gastrointestinal toxicity: two case reports from the FLARE/GFPC 03-2013 study. J Clin Pharm Ther 2016; 41: 447–8.

72 Sunela K, Barlund M. Treatment and prevention of iphosphamide-induced encephalopathy. Duodecim; laaketieteellinen aikakauskirja 2016; 132: 314–7 [in Finnish].

73 Tsuda T, Kyomori C, Mizukami T, Taniyama T, Izawa N, Horie Y, *et al*. Infusion site adverse events in breast cancer patients receiving highly emetic chemotherapy with prophylactic anti-emetic treatment with aprepitant and fosaprepitant: a retrospective comparison. Mol Clin Oncol 2016; 4: 603–6.

74 Jones JD, Speer T, Comer SD, Ross S, Rotrosen J, Reid MS. Opioid-like effects of the neurokinin 1 antagonist aprepitant in patients maintained on and briefly withdrawn from methadone. Am J Drug Alcohol Abuse 2013; 39: 86–91.

75 Mir O, Durand JP, Boudou-Rouquette P, Giroux J, Coriat R, Cessot A, *et al*. Interaction between serotonin reuptake inhibitors, 5-HT3 antagonists, and NK1 antagonists in cancer patients receiving highly emetogenic chemotherapy: a case-control study. Support Care Cancer 2012; 20: 2235–9.

76 Nakano K, Ushijima K, Ando H, Fujimura A, Morita T. Enhancement of anticoagulant effect of warfarin in a bladder cancer patient during treatment with gemcitabine and cisplatin. Int Cancer Conf J 2015; 4: 254–7.

77 Ohno Y, Yamada M, Yamaguchi R, Hisaka A, Suzuki H. Persistent drug interaction between aprepitant and warfarin in patients receiving anticancer chemotherapy. Int J Clinical Pharm 2014; 36: 1134–7.

78 Walsh SL, Heilig M, Nuzzo PA, Henderson P, Lofwall MR. Effects of the NK1 antagonist, aprepitant, on response to oral and intranasal oxycodone in prescription opioid abusers. Addict Biol 2013; 18: 332–43.

79 Yano R, Kurokawa T, Tsuyoshi H, Shinagawa A, Sawamura Y, Matsunaga A, *et al*. Transient elevation of international normalized ratio during cisplatin-based chemotherapy in patients who are taking warfarin. Ann Pharmacother 2011; 45: e55.

80 Inagaki Y, Suzuki T, Saeki S, Tsushita N, Sakai T, Kato T, *et al*. Construction of the system of treatment for deep venous thrombosis with malignant tumor in Anjo Kosei Hospital. Ann Oncol 2015; 26: vii139–NaN.

81 Okada N, Watanabe H, Kagami S, Ishizawa K. Ifosfamide and etoposide chemotherapy may interact with warfarin, enhancing the warfarin-induced anticoagulant response. Int J Clin Pharmacol Ther 2016; 54: 58–61.

82 Takaki J, Ohno Y, Yamada M, Yamaguchi Y, Hisaka A, Suzuki H. Assessment of drug–drug interaction between warfarin and aprepitant and its effects on PT-INR of patients receiving anticancer chemotherapy. Biol Pharm Bull 2016; 39: 863–8.

83 Kacevska M, Robertson GR, Clarke SJ, Liddle C. Inflammation and CYP3A4-mediated drug metabolism in advanced cancer: impact and implications for chemotherapeutic drug dosing. Expert Opin Drug Metab Toxicol 2008; 4: 137–49.

84 de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: ontogeny and drug disposition. Clin Pharmacokinet 1999; 37: 485–505.

85 Prasad B, Gaeadigk A, Vrana M, Gaedigk R, Leeder J, Salphati L, *et al*. Ontogeny of hepatic drug transporters as quantified by LC-MS/MS proteomics. Clin Pharmacol Ther 2016; 100: 362–70.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13322/suppinfo

Appendix S1 Literature search
Table S1 Search strategy
Table S2 List of grey literature sources searched
Appendix S2 Publication selection, data extraction and quality assessment procedures
Appendix S3 Study results

Table S3 Downs and Black quality assessment for publications evaluating pharmacokinetic drug interactions between aprepitant or fosaprepitant and antineoplastic drugs
Table S4 Downs and Black quality assessment for publications evaluating pharmacokinetic drug interactions between aprepitant or fosaprepitant and non-antineoplastic drugs
Table S5 Downs and Black quality assessment for publications evaluating clinical drug interactions between aprepitant or fosaprepitant and antineoplastic and non-antineoplastic drugs
Table S6 Studies evaluating pharmacokinetic drug interactions between aprepitant or fosaprepitant and antineoplastic agents
Table S7 Studies evaluating pharmacokinetic drug interactions between aprepitant or fosaprepitant and non-antineoplastic agents
Table S8 Drug interaction studies evaluating potential adverse events resulting from potential drug interactions between aprepitant or fosaprepitant and an antineoplastic agent
Table S9 Drug interaction studies evaluating potential adverse events resulting from potential drug interactions between aprepitant or fosaprepitant and a non-antineoplastic agent
Table S10 Drug interaction probability scale evaluation for case reports
Appendix S4 Victim drug routes of metabolism, transporters where victim drugs are substrates and renal elimination